UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 15, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

MEMORANDUM

SUBJECT: **PHOSMET - REREGISTRATION CASE NO. 0242** - Toxicology Chapter for the Reregistration Eligibility Decision Document on Phosmet

P.C. CODE: 059201 DP BARCODE NO.: D237450
TOX. CHEM. NO.: 543 SUBMISSION NO.: S523996
CAS NO.: 732-11-6

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Attached please find the Toxicology Chapter for the Reregistration Eligibility Decision Document on phosmet. This chapter is to be incorporated into the HED's RED for reregistration of Phosmet.

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Human Health Assessment: Phosmet

1. Toxicology Assessment Hazard/Dose-Response Assessment

The toxicological database for Phosmet is not complete but will support reregistration. There are 4 data gaps, a 21-day dermal toxicity study, an acute neurotoxicity study, a subchronic neurotoxicity study and a dermal sensitization study. These studies are considered to be confirmatory data and should be submitted as soon as possible.

a. Acute Toxicity

Table 1 below summarizes the results of acute toxicity studies on phosmet and the different routes of administration.

Table 1: Acute Toxicity Data for Phosmet (TGAI)

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Test	Results	TOXCAT
Oral LD50 - rat (MRID 00046189)	LD_{50}(male) = 113 (101-127) mg/kg LD_{50}(female) = 113 (98-130) mg/kg	II
Dermal LD50 - Rabbit (MRID 00046190)	LD_{50} > 5000 mg/kg	IV
Inhalation LC50 (MRID 00063197)	LC_{50} > 0.152 mg/l No death occurred.	II
Eye irritation (MRID 00046192	Moderate eye irritation.	III
Dermal Irritation (MRID 00046191)	No irritation.	IV
Acute Neurotoxicity-hen (MRID 00043469) Acute Neurotoxicity-hen (MRID 00046187) Acute Neurotoxicity-hen (MRID 00081431) Acute Neurotoxicity-hen (MRID 00109652)	Negative* EQUIVOCAL Negative* Negative*	

***Studies classified as supplementary but have valid scientific information.**

b. Subchronic Toxicity

Oral Study in Rats:

1) In a 16-week subchronic feeding study in rats (MRID 00081429), Phosmet was administered to Charles River weanling albino rats to a high-dose group (10 males, 10 females) at 800 ppm (O - 3 weeks), 1600 ppm (4 - 9 weeks), 2000 ppm (10th week), 3000 ppm (llth week) and 6000 ppm (12th - 16th week) and to a low-dose group (10 males, 10 females) at 450 ppm (0 - 3 weeks), 900 ppm (4 - 9 weeks) and 1120 (10th - 16th week). The dosages of 450, 800, 900, 1120, 1600, 2000, 3000 and 6000 ppm are approximately 45, 80, 90, 112, 160, 200, 300 and 600 mg/kg/day (by standard conversion methods). A control group of 10 males and 10 females was included.

Two females in the high-dose group died during the 16th week. Starting about week 3, all treated rats exhibited nervous behavior. By the 4th week tremors were observed in both groups. By the 5th or 6th week diarrhea was noted. Bulging eyes were noted in the high-dose group beginning at the 12th week. Body weight of rats in the high-dose group was 67-68% of controls at the 15th week. Body weight of males and females in the low-dose group was 92% and 78% of controls at the 15th week. Decreased food intake was observed in high-dose males and females. RBC ChE was totally inhibited in both groups. Plasma ChE was decreased 54-89% in both groups. Brain ChE was inhibited 75-84% in both groups. Liver and adrenal absolute and relative weights were increased at the high-dose. Hepatic degenerative changes and some adrenal hypertrophy were observed histologically in the high-dose group. The ChE inhibition LOEL is 450-1120 ppm. The ChE inhibition NOEL was not determined. The Systemic Toxicity LOEL is 450-1120 ppm based on clinical signs and body weight decreases. The Systemic Toxicity NOEL was not determined.

2) In a 14-week subchronic feeding study (MRID 00080556, 00081428, 00075419, 00088282, 00081426), Phosmet (98%) was administered to weanling albino rats at dose levels of 0, 20, 100 and 500 ppm (corresponding to 0, 2, 10 and 50 mg/kg/day) in the diet.

One male in the 500 ppm group died at week 3. Body weight of males in the 500 ppm group was 85% of control values at 14 weeks. Erythrocyte ChE was almost entirely (95-100%) inhibited in rats in the 500 ppm group by the 3rd or 4th week. Plasma ChE was inhibited 80% in females in the 500 ppm group from the 4th week on. Plasma ChE was inhibited 50% in males in the 500 ppm group. Erythrocyte ChE was inhibited 50% in males and females in the 100 ppm group. Plasma ChE was inhibited 15% in males and females in the 100 ppm group. Brain ChE was inhibited 75-80% in rats in the 500 ppm group, 40% in rats in the 100 ppm group and 5-10% in rats in the 20 ppm group.

The ChE inhibition LOEL is 100 ppm (10 mg/kg/day). The ChE inhibition NOEL is 20 ppm (2 mg/kg/day). The LOEL is 500 ppm (50 mg/kg/day) based on decreased body weight. The Systemic Toxicity NOEL is 100 ppm (10 mg/kg/day). [This study is classified as unacceptable; however, it contains valid scientific information]

Oral Study in Dogs

In a 14-week subchronic feeding study (MRID 00080556, 00081428, 00075419, 00088282, 0081426), Phosmet (98%) was administered to groups of 4 male and 4 female beagle dogs at dose levels of 0, 10, 75 or 563 ppm (approximately 0, 0.25, 1.875 and 14.075 mg/kg/day in the diet (by standard conversion methods).

Erythrocyte ChE was 100% inhibited in dogs in the 563 ppm group by 6 weeks. Plasma ChE was inhibited 10-50% in dogs in the 563 ppm group by 10-13 weeks. Brain ChE was inhibited 95% in dogs in the 563 ppm group. The ChE inhibition LOEL is 563 ppm (14.075 mg/kg/day). The ChE inhibition NOEL is 75 ppm (1.875 mg/kg/day). The Systemic Toxicity LOEL was not determined. The Systemic Toxicity NOEL is 563 ppm (14.075 mg/kg/day).

Dermal Study in Rabbits

In a 21-day subchronic dermal toxicity study (MRID 40538101) groups of 5 male and 5 female Hra:(NZW)SPF rabbits were dermally administered 0, 10, 100 or 1000 mg/kg/day technical Imidan (Phosmet, Lot #492-42-8) in mineral oil. The rabbits were exposed for approximately 6 hours/day, 5 days/week for 3 weeks.

No dermal toxicity was observed. The vehicle apparently caused dermal inflammation observed during histopathological examination and questions exist as to the appropriateness of the vehicle (possibly limiting absorption of the test material). Both plasma and erythrocyte cholinesterase were inhibited in males (20 and 25%, respectively, and females (35 and 22%, respectively) in the 1000 mg/kg/day group. Slight decreases in cholinesterase activity were observed in the 100 mg/kg/day group but the biological relevance is questionable. The vehicle (mineral oil) probably decreased absorption, therefore the utility of the data is questionable. Kidney absolute weights were significantly decreased in all male treated groups. Kidney to brain weight ratios were significantly decreased at all dose levels. The Systemic Toxicity NOEL/LOEL could not be established because of the possible effect of the vehicle on absorption. [This study, although classified as unacceptable, contains valuable scientific information]

Neurotoxicity Study

A subchronic neurotoxicity study in a mammalian species was not available for review.

c. Chronic Toxicity/Carcinogenicity

Oral Study in Rats

1) In a 2-year chronic toxicity/carcinogenicity study (MRID 41916401) Phosmet (Lot # EHC-0866-24, WRC-4921-42-8) was administered to Sprague-Dawley Crl:CD(R) SD BR rats in the diet at 0, 20, 40, 200 or 400 ppm (400 ppm terminated at 12 months) (equivalent to 0, 1.1, 1.8, 9.4 and 23 mg/kg/day in males and 0, 1.1, 2.1, 10.9 and 27 mg/kg/day in females).

At 20 ppm there was marginal RBC cholinesterase (ChE) inhibition (16%) noted at 6 months in males only. At 40 ppm RBC (about 15-20%) and serum ChE (5-36%- M; 15-25%- F) was inhibited in both males and females. Brain ChE was inhibited (>34%) in males and females at 200 ppm. The ChE inhibition LOEL was $\leq$ 20 ppm based on RBC ChE in males (marginal - only at 6 months). The ChE inhibition NOEL was < 20 ppm.

Systemic toxicity was limited to increased incidence of fatty change in the liver of males at all doses. In addition, at 200 ppm and above (males) there were increases in the incidences of depressed hepatic foci, hyperkeratosis of the stomach; (females) fatty change in the liver, mineralization of the thyroid. At 400 ppm (males and females) body weight and body weight gain were decreased; (females) decreased kidney weight and increased BUN. The Systemic Toxicity LOEL is $\leq$ 20 ppm based on an increased incidence of fatty change in the liver of males. the Systemic Toxicity NOEL < 20 ppm. At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. This study was determined to be tested at adequate but not excessive dose levels by the HED Cancer Peer Review committee (meeting November 17, 1993) based on ChE inhibition.

2) In a 2-year chronic toxicity/carcinogenicity study (MRID 00062651, 00076436, and 00080431),Imidan (Phosmet) was administered to groups of 25 Charles River rats in the diet at 20, 40 or 400 ppm (approximately 1, 2 or 20 mg/kg/day by standard conversion methods). Body weight gain was slightly decreased in males in the 400 ppm group. Plasma, erythrocyte and brain cholinesterase activity was decreased in

rats in the 400 ppm group. Minimal liver cell alteration was observed in rats in the 400 ppm group. Neoplasia found and diagnosed were judged to be unrelated to treatment. The cholinesterase inhibition LOEL is 400 ppm (20 mg/kg/day). The cholinesterase inhibition NOEL is 40 ppm (2 mg/kg/day). The Systemic Toxicity LOEL is 400 ppm based on liver cell alteration. The Systemic Toxicity NOEL is 40 ppm.

Oral Study in mice

In a 2-year carcinogenicity study (MRID 00141659, 00160114, 40595501), groups of 60 male and 60 female B6C3F1-Crl-BR mice were administered 0, 5, 25 or 100 ppm (approximately 0.75, 3.75 or 15.0 mg/kg/day by standard conversion methods) of Phosmet (94.70%, Lot #EHC-0139-37/WRC-4921-3131) in the diet. There was an increased incidence of convulsions in males in the 25 and 100 ppm groups. Cholinesterase activity was variable and inconsistent, therefore NOEL/LOELs could not be determined for cholinesterase activity. The absolute liver weight was increased in males in the 100 ppm group. The absolute and relative liver weight was increased in females in the 25 and 100 ppm group. There was an increase of degenerative vacuolation of individual liver cells and foci and vacuolated or clear cells in the liver of males in the 100 ppm group. Males in the 100 ppm group also exhibited perivasculitis of muscle, hyperplasia of stomach mucosa and testicular atrophy. Females in the 100 ppm group exhibited midzonal degenerative vacuolation of the liver, necrotizing inflammation of the stomach and duodenum and myometrial atrophy. There was an increased incidence of hepatocellular tumors in male and female mice in the 100 ppm group. The cholinesterase inhibition NOEL/LOEL could not be established. The Systemic Toxicity LOEL is 25 ppm (3.75 mg/kg/day) based on convulsions in males and increased liver weights in females. The Systemic Toxicity NOEL is 5 ppm (0.75 mg/kg/day). There was positive evidence for carcinogenicity.

Oral Study in dogs

In a dog feeding study (MRID 00076436, 00062651, and 00080431), beagle dogs, 3 per sex were treated with 0 (control), 20, 40 or 400 ppm (0, 0.5, 1.0 or 10 mg/kg/day) of Phosmet in the diet for 104 weeks. There were no treatment related systemic effects at any dose up to and including the high dose of 400 ppm. The Systemic Toxicity LOEL is greater than 400 ppm. The Systemic Toxicity NOEL is equal to or greater than 400 ppm. Erythrocyte (greater than 70%;) and brain (greater than 40%) cholinesterase were inhibited in males and females only at the high dose of 400 ppm The cholinesterase inhibition LOEL is 400 ppm. The cholinesterase inhibition NOEL is 40 ppm (1.0 mg/kg/day) based on inhibition of RBC and brain cholinesterase.

d. Developmental Toxicity

Oral study in Rats

In a developmental toxicity study (MRID 41962902), groups of 24 Wistar rats were administered 0, 5, 10 or 15 mg/kg/day of Phosmet (96.4%, Lot # CIF 2402) during gestation days 7-16. Treatment related maternal toxicity was observed at 15 mg/kg/day and was manifested as an increased occurrence of clinical signs (piloerection, tremors, salivation, signs of urinary incontinence and subdued mood) and decreased body weight gain and food consumption during the exposure period (GD 7-16). Decreased body weight gain was also observed at 10 mg/kg/day. The Maternal Toxicity LOEL is 10 mg/kg/day based on decreased body weight gain. The Maternal Toxicity NOEL is 5 mg/kg/day. No developmental toxicity was observed. The Developmental Toxicity LOEL is greater than 15 mg/kg/day. The Developmental Toxicity NOEL is equal to or greater than 15 mg/kg/day.

Oral Study in Rabbits

In a developmental toxicity study (MRID 41962901) groups of 20 New Zealand White rabbits were administered 0, 2, 5 or 15 mg/kg/day of Phosmet (96.4%, Lot #CIF 2402) during gestation days 7-19. Maternal toxicity was observed at 15 mg/kg/day and was manifested as an increased occurrence of clinical signs (unsteady gait, shaking, salivation and irregular breathing), possible treatment-related mortality and decreased body weight gain during the exposure period (GD 7-19). The Maternal Toxicity LOEL is 15 mg/kg/day based on clinical signs of toxicity and decreased body weight gain. The Maternal Toxicity NOEL is 5 mg/kg/day. There were increased incidences of skeletal variations consisting of reduced ossification of the 6th sternebra, asymmetrical development of the 2nd sacral vertebra and increased pes score without reduction in fetal weight was observed at 15 mg/kg/day. The Developmental Toxicity LOEL is 15 mg/kg/day based on skeletal variations. The Developmental Toxicity NOEL is 5 mg/kg/day.

Oral Study in Monkeys

In a developmental toxicity study (MRID 00043397), groups of 7 Macaca mulatta monkeys were administered Phosmet (technical, Lot# 1266-76) in a 50% honey solution at dose levels of 2.0, 4.0 or 8.0 mg/kg/day on gestation days 22-32. Pregnancies were terminated by cesarean section on the 84th day of gestation.

Six of 7 monkeys at 8.0 mg/kg/day produced anatomically normal fetuses. One monkey aborted. Seven of 7 monkeys at 4.0 mg/kg/day produced anatomically normal fetuses.

Five of 7 monkeys at 2.0 mg/kg/day produced anatomically normal fetuses. One monkey aborted and one monkey resorbed the fetus. The body weights, x-rays, organ weights and organ to body weight ratios, as well as crown-rump lengths of the fetuses were within normal limits. Maternal body weight and hematology showed no compound related effects. The LOELs for Maternal and Developmental Toxicity were not determined. The NOELs for Maternal and Developmental Toxicity are equal to or greater than 8.0 mg/kg/day.

e. Reproductive Toxicity

In a two generation reproduction study (MRID 41520001), Sprague-Dawley (Crl:CD SD BR) rats, 25 per sex were treated with 0 (control), 20, 80 or 300 ppm (equal to 0, 1.5, 6.1 or 23.4 mg/kg/day) of Phosmet (95.%, Lot #EHC-0866-14; WRC-4921-42- 8) in the diet continuously. Parental toxicity consisted of RBC ChE inhibition at 20 ppm (6-16%), 80 ppm (>37%), and 300 ppm (>74%). Serum ChE was inhibited at 80 ppm (34%) and 300 ppm (65%). There were clinical signs (tremors) noted at 300 ppm). The parental LOEL is less than 20 ppm (1.5 mg/kg/day). The Parental Systemic NOEL is equal to or less than 20 ppm (1.5 mg/kg/day). Reproductive/Developmental toxicity consisted of decreased fertility, number of live pups/litter, pup weights, lactation index and fertility index (e.g., 88% versus 48%, control and high dose). The Reproductive/Developmental Toxicity LOEL is 80 ppm (6.1 mg/kg/day). The Reproductive/Developmental Toxicity NOEL is 20 ppm (1.5 mg/kg/day) based on decreased fertility, number of live pups/litter, pup weights, lactation index and fertility index.

f. Mutagenicity

Ames Test

The mutagenic potential of phosmet (95.7%, Lot #WRC 1020141-1, ECH-0829-03) was studied in 5 histidine auxotroph bacterial strains derived from Salmonella typhimurium (TA98, TA100, TA1535, TA1537 and TA1538), according to the test method of Ames (MRID 00164884). Phosmet was tested at 56, 313, 625, 1250 and 2500 μg/plate under nonactivated and activated conditions. The dosage range used was based on an initial cytotoxicity study in which doses were evaluated at 20 to 10,000 μg/plate. Dose-related increases in reversion to histidine prototropy was observed at nonactivated doses of > 625 μg/plate and at S9-activated doses of > 31 μg/plate. These results indicate that the mutagenic activity of Phosmet was not dependent on metabolic conversion.

Chromosome Damage

The mutagenic potential of Phosmet (95.7%, Lot # 10201-41-4) was studied using a chromosomal sister chromatid exchange (SCE) assay with mouse lymphoma cells (MRID 00164885). Five doses were evaluated (40, 50, 60, 80 and 100 μg/ml without activation and 8, 10, 15, 20 and 40 μg/ml with S9 activation). Nonactivated phosmet at 80 and 100 μg/l increased the total number of aberrations and frequency of aberration per cell to a level that was equal to or greater than the nonactivated positive control, ethylmethanesulfonate. In the presence of S9 activation, cytotoxicity was more severe and there was no evidence of a clastogenic effect. In contrast, both the nonactivated and S9-activated test material induced dose-related increases in SCEs at all assayed levels (40-100 μl/ml -S9; 8-40 μl/ml +S9). Phosmet is, however, considered a direct acting clastogen.

DNA Repair

The mutagenic potential of Phosmet (95.7%, Lot #10201-41-1) was studied using the DNA assay in human fibroblasts (MRID 00164887). Growing human fibroblasts were dosed for 1 hour at 0.25 to 1 mg/ml of the test material and solvent control (DMSO) with and without S9 activation. The positive control was assayed at 1.3 μl/ml with S9 activation only. Under the conditions of the nucleoid sedimentation assay, phosmet, with or without S9 activation, did not induce DNA damage in human fibroblasts. Dimethylnitrosamine, in the presence of S9 activation, demonstrated the sensitivity of the test system to detect DNA damage.

Mouse Lymphoma Forward Mutation

The mutagenic potential of Phosmet (95.7%, Lot #WRC 1020141-1, ECH-0829-03) was studied using the mouse lymphoma assay (MRID 00164886). Five dose levels were assayed (20, 40, 60, 80 and 100 μg/ml without S9 and doses of 4-8 μg/ml or 10-40 μg/ml were assayed with S9 activation). The results showed dose-related increases in mutation frequencies under nonactivated conditions that ranged from a 1.6-fold increase at the lowest reactive dose (60 μg/ml) to a 5.8-fold increase at the highest dose (100 μg/ml). The dose-related mutagenic effects induced by phosmet were confirmed in a repeat study where the fold increase in mutation ranged from 10.7 at the highest dose (100 μg/ml; cell survival = 3%) to 1.4 at the lowest dose (40 μg/ml). The lack of a mutagenic effect suggests that Phosmet's ability to cause gene mutations and chromosomal aberrations (see above) may be blocked or reduced in the presence of exogenous metabolic activation.

Cell Transformation

The mutagenic potential of Phosmet (95.7%, Lot #WRC 1020141-1, ECH-0829-03, T12819) was studied using the BALB/3T3 transformation assay (MRID 00164888). Nonactivated dose levels of 4, 6, 8, 10, 12 and 14 μg/ml were tested. The results showed that > 2-fold increases in the total number of foci when compared to the solvent control, were scored at 6, 8 and 14 μg/ml. At the 8 μg/ml level, 7 of 15 flasks had foci, in contrast to 2/15 for the solvent control. The number of flasks with foci at 8 μg/ml was only slightly less than the number calculated for the positive control 3-methylcholanthene at 1.0 μg/ml. The test results satisfy the generally accepted criterion for a positive response in this assay (> 2-fold increase in foci/dish).

Micronucleus

The mutagenic potential of Phosmet (95.5%, Lot # 11694), was studied using the mouse micronucleus assay (MRID 40199401). Phosmet at a dose level of 17 mg/kg, was administered to groups of 5 male and 5 female 6-12 week old CD-1 mice per sacrifice interval. A vehicle control and positive control group using 74 mg/kg cyclophosphamide was included. The mice, receiving test material or vehicle control, were sacrificed at 24, 48 and 72 hours after compound administration. The positive control was sacrificed at 24 hours. One thousand polychromatic erythrocytes (PCEs) per animal were scored for the number of micronucleated polychromatic erythrocytes. Phosmet did not cause a clastogenic effect in the bone marrow cells assayed at 24, 48 or 72 hours. Decreased PCEs to total erythrocytes were seen in the preliminary assay at $\geq$15 mg/kg and at 17 mg/kg in the main study. Cyclophosphamide demonstrated the

sensitivity of the assay to detect a clastogenic response. Based on a preliminary toxicity study and the cytotoxicity response noted in the assay, the dose selected was adequate.

g. Metabolism

The absorption, distribution, metabolism, and excretion of R-1504 (Phosmet) were studied in groups of male and female Sprague-Dawley rats administered a single oral gavage dose of 1 or 25 mg/kg [14C]R-1504 or a 14-day repeated oral dosing of 1 mg/kg unlabeled R-1504 followed by a single dose of 1 mg/kg [14C]-labeled R-1504 on day 15 (MRID 41296001, 41425701). The pharmacokinetics of [14C]R-1504 were studied in rats administered a single oral dose of 1 or 25 mg/kg (males and females) of 14C-labeled test material.

[14C]R-1504 was rapidly absorbed, distributed, metabolized, and eliminated in rats for all dosing regimens. Most of the radioactivity was recovered within 24 hours in the urine (68.9-82.6% of the administered dose) and feces (4.5-9.9%) of all dose groups. There appeared to be a slight saturation of R-1504 in the high-dose group as indicated by the somewhat increased recovery of radioactivity in the feces of the 25-mg/kg animals (9.4-13.4% of dose) compared to the 1-mg/kg animals (single and repeated dosing) (6.3-8.0%). There was wide distribution of R-1504, and the tissues contained low levels of radioactivity ($\leq$ l% of the administered dose) in all dose groups; the highest activity was in the liver and whole blood and lowest activity in the fat and bone (on both a concentration and percent-of-dose basis). These data indicate that R-1504 and/or its metabolites do not bioaccumulate to an appreciable extent. The absorption of R-1504 appears to be rapid in rats because the peak blood levels of radioactivity occurred 0.5 hours after oral exposure to a single dose of 1 or 25 mg/kg R1504. The metabolism of R-1504 appears to be relatively complete and rapid. The two major radioactive bands in the urine sample were identified as N-(methylsulfinylmethyl)phthalamic acid (PaAMS[O]M) and N-(methylsulfonylmethyl)phthalamic acid (PaAMS[02]M); however, the 11 minor bands in the urine were not identified. Although nine radioactive components were characterized in feces, no attempt was made to identify these fecal metabolites. Furthermore, it was not determined if the parent compound was recovered in the urine or feces. Therefore, based on results, it is difficult to determine whether there were any remarkable sex-, dose-, or treatment-related differences in the absorption, distribution, metabolism, and elimination of [14C]R-1504 in rats. The only sex-related differences observed in the urinary excretion of PaAMS(O)M and PaAMS(02)M metabolites were as follows: the 1-mg/kg females (single and repeated dosing) had a higher recovery of PaAMS(O)M compared to males and all dosed males had a higher recovery of PaAMS(02)M compared to females. These studies also showed that single oral

administration of 1 and 25 mg/kg R-1504, as well as repeated dosing with 1 mg/kg/day, did not induce any apparent treatment-related clinical effects.

h. Dermal Absorption

In a dermal absorption study (MRID 40122201), Phosmet (Imidan 50-WP, 50%, Lot #10 RSEE 300 10) was applied to the shaved skin on the back of 4 male Sprague-Dawley (CD) rats/group. Dilutions used were 1:2, 1:10 and 1:100 applied at a rate of 300 μl rat. Administered doses were 2.67, 0.52 and 0.058 mg/cm2 skin. The dosing solutions contained 20-50 μCi of labeled compound. The radioactive test material had a specific activity of 26.6 mCi/mmol and was 97% pure. Phosmet was poorly absorbed when applied to the shaved skin of rats. The percent of radioactive dose found in the carcass, skin, urine, feces, and blood (combined) after 24 hours was 0.9, 3.8, and 11.8% of administered doses of 2.67, 0.52 and 0.058 mg/cm skin, respectively. The skin at the dosing site contained much of the radioactivity. The amount in the carcass and excreta reached a maximum at 24 hours and accounted for 7.9, 1.7 and 0.3% of the administered radioactivity at the low-, mid- and high-doses, respectively. Excretion of the absorbed radioactivity was primarily urinary; 0.1% of the high-dose (1:2 dilution), 1.1% of the mid-dose (1:10 dilution), and 5.4% of the lowdose (1:100 dilution) radiolabel was found in the urine between 10 and 24 hours. Much lesser amounts were found in the feces.

i. Cancer Classification and Basis:

Carcinogenicity:

The carcinogenicity issue has been discussed by the Health Effects Division Cancer Peer Review Committee. The Committee agreed that "phosmet should be classified as a "Group C", possible human carcinogen, and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk".

"This decision was based on an increased incidence of liver tumors in male B6C3F1 mice at the high dose, that was statistically significant by pair-wise comparison, with a statistically significant trend and which also had an apparent early onset. Female mice had a significant dose-related trend for liver tumors, and for mammary gland adenocarcinomas, as well. There was no evidence for carcinogenicity in an acceptable study in rats" (report dated May 25, 1994).

j. Reproductive and Developmental Toxicity:

The reproductive and developmental toxicity issues had been recently addressed by the HED RfD/QA Committee (report dated May 11, 1994).

Developmental Neurotoxicity: In the attempt to develop a weight-of-the-evidence recommendation on the need for developmental neurotoxicity testing with phosmet, all the following information was considered:

1) Evidence that supports requiring a developmental neurotoxicity study:

Phosmet is a neurotoxic organophosphate associated with plasma, RBC and brain cholinesterase inhibition in various species. According to the one-liners, there is a positive acute delayed neurotoxicity study in hens with phosmet, and a neurotoxic esterase study which is also positive. The delayed neurotoxicity was not, however, repeated in subsequent studies. Adequate characterization of the cholinesterase inhibition has been conducted, although not in pregnant females or their offspring.

Phosmet may disrupt neuroendocrine function, as evidenced by reductions in fertility, mating performance in the two-generation reproduction study in rats, reduced testes and ovary weights, and histopathological evidence of moderately decreased spermatogenesis. Reproductive function was impaired more severely in the second generation than the first.

2) Evidence that does not support asking for a developmental neurotoxicity study:

No evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either Wistar rats or New Zealand white rabbits, at maternal gavage doses up to 15 mg/kg/day. The maternal doses were sufficient to elicit clinical signs of toxicity in the dams. (It is noted that assessment of differential response of offspring versus adults to cholinesterase inhibition following treatment with phosmet was not conducted.)

No evidence of alterations to brain weight or histopathology were observed in the chronic toxicity studies in rats, mice, and dogs.

3) Other Factors:

Acute and subchronic neurotoxicity studies in rats have not yet been submitted. Furthermore, comparative cholinesterase measurements in adult and neonatal animals

(rats) have not been assessed.

Based on the above, the Committee agreed that there was insufficient data to determine the need for a developmental neurotoxicity in rats. Such a determination would depend on the results of an acute and/or subchronic neurotoxicity study in rats, in particular, upon the neuropathology data, which are more sensitive in detecting treatment-related effects than the data from a standard subchronic or chronic studies. Neither of these two neurotoxicity studies have been submitted to the Agency yet.

The inability to assess the need for a developmental neurotoxicity study is considered a potential data gap for the assessment of hazard to infants.

FQPA Considerations:

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to ... "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for phosmet was evaluated by the Hazard Identification Committee. The Committee concluded the following:

Adequacy of data: The data base for phosmet included an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits, meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. However, because of the lack of the necessary information, required to assess the need for a developmental neurotoxicity study in rats, it was determined that a data gap exists for the assessment of hazard to infants and children.

Susceptibility: The available data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to phosmet.

Uncertainty factor: The inability to assess the need for a developmental neurotoxicity study is considered a data gap for the assessment of hazard to infants and children.

The Committee evaluated the data as described and concluded that the 10-fold uncertainty factor for the protection of infants and children can be reduced to 3-fold for the following reasons: 1) the database for the assessment of toxicity to infants and children is complete, 2) the data base, which includes acceptable developmental toxicity studies in two species and a two-generation reproduction study in rats, demonstrate no evidence of increased sensitivity to young animals following pre- and/or postnatal exposure to phosmet, 3) results from studies conducted to evaluate the potential for delayed neurotoxicity and neurotoxic esterase assays did not support classification of phosmet as a delayed neurotoxicant.

Nevertheless, since acute and subchronic neurotoxicity studies in rats have not been submitted to the Agency at the time of this review, a full characterization of the neuropathological potential for phosmet is not available. Positive results from these studies could potentially lead to a data requirement for a developmental neurotoxicity study in rats. This is considered a potential data gap for the assessment of hazard to infants and children, for which a 3-fold uncertainty factor was recommended.

k. HAZARD IDENTIFICATION:

The Health Effects Division Hazard Identification Committee met on September 4, 1997 to evaluate the existing and/or recently submitted toxicology data in support of phosmet reregistration, identify toxicological endpoints and dose levels of concern appropriate for use in risk assessments for different exposure routes and duration, and assess/reassess the reference dose (RfD) for this chemical.

Phosmet had already been evaluated by the HED RfD/QA Committee on March 3, 1994 (report dated May 11, 1994). Therefore, this Hazard Identification Committee report should be considered in conjunction with the RfD Committee report of March 3, 1994.

Dermal Absorption:

In a dermal absorption study (MRID 40122201), phosmet (Imidan 50-WP, 50%, Lot #10 RSEE 300 10) was applied to the shaved skin on the back of 4 male Sprague-Dawley (CD) rats/group. Dilutions used were 1:2, 1:10 and 1:100 applied at a rate of 300 μl rat. Administered doses were 2.67, 0.52 and 0.058 mg/cm^2 skin. The dosing solutions contained 20-50 uCi of labeled compound. The radioactive test material had a specific activity of 26.6 mCi/mmol and was 97% pure. Phosmet was poorly absorbed when applied to the shaved skin of rats. The percent of radioactive dose found in the carcass, skin, urine, feces, and blood (combined) after 24 hours was 0.9, 3.8, and 11.8% of administered doses of .67, 0.5% and 0.058 mg/cm skin, respectively. The skin at the dosing site contained much of the radioactivity. The amount in the carcass and excreta reached a maximum at 24 hours and accounted for 7.9, 1.7 and 0.3% of the administered radioactivity at the low-, mid- and high-doses, respectively. Excretion of the absorbed radioactivity was primarily urinary; **0.1%** of the high-dose (1:2 dilution), **1.1%** of the mid-dose (1:10 dilution), and 5.4% of the lowdose (1:100 dilution) radiolabel was found in the urine between 10 and 24 hours. Much lesser amounts were found in the feces.

The Committee estimated that the dermal absorption rate is about 10%.

Based on comprehensive evaluation of the toxicology data available on phosmet, the following toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories indicated below.

Where no appropriate data have been identified for a particular duration or exposure scenario, or if a risk assessment is not warranted, this is noted. Levels of uncertainties associated with intraspecies variability, interspecies extrapolation, route

to route conversion, or variable durations extrapolation are also addressed.

Based on the exposure/use profile for phosmet, the Committee determined that the risk assessments indicated below are required.

DIETARY EXPOSURE:

Chronic Dietary Exposure-Reference Dose (RfD):

Reference Dose (R_fD): 0.003 mg/kg/day.

Critical Study: Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

Executive Summary:

In a 2-year chronic toxicity/carcinogenicity study (MRID 41916401) phosmet (Lot # EHC-0866-24, WRC-4921-42-8) was administered to Sprague-Dawley Crl:CD(R) SD BR rats in the diet at 0, 20, 40, 200 or 400 ppm (400 ppm terminated at 12 months) (doses of: males - 0, 1.1, 1.8, 9.4 and 23 mg/kg/day; females - 0, 1.1, 2.1, 10.9 and 27 mg/kg/day) for 2 years.

At 20 ppm there was marginal RBC cholinesterase (ChE) inhibition (16%) noted at 6 months in males only. At 40 ppm RBC (about 15-20%) and serum ChE (5-36%- M; 15-25%- F) was inhibited in both males and females. Brain Che was inhibited (>34%) in males and females at 200 ppm. **The LOEL for ChE inhibition was $\leq$ 20 ppm based on RBC ChE in males (marginal - only at 6 months). The NOEL for (ChE) inhibition was < 20 ppm**.

Systemic toxicity was limited to increased incidence of fatty change in the liver of males at all doses. In addition, at 200 ppm and above (males) there were increases in the incidences of depressed hepatic foci, hyperkeratosis of the stomach; (females) fatty change in the liver, mineralization of the thyroid. At 400 ppm (males and females) body weight and body weight gain were decreased; (females) decreased kidney weight and increased BUN. **The systemic LOEL is $\leq$ 20 ppm based on an increased incidence of fatty change in the liver of males. the systemic NOEL < 20 ppm.** At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. This study was determined to be tested at adequate but not excessive dose levels by the HED Cancer Peer Review committee (meeting November 17, 1993) based on ChE inhibition.

Endpoint and Dose Level Selected for use in risk assessment: NOEL = 1.1

mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. The use of a UF of 100 was justified based on the availability of a chronic toxicity study in a second species (MRID No. 00062651, 00075419, 00076436, 00080431, 00080556) and a reproductive toxicity study in rats (MRID No. 41520001) in accordance with the rules established by the Agency-IRIS (Integration Risk Information System) Work Group.

Pursuant to the FQPA, an additional UF of 3 was recommended to account for the lack of acute and subchronic neurotoxicity studies in rats. A full characterization of the neuropathological potential for phosmet is not available. Positive results from these studies could potentially lead to a data requirement for a developmental neurotoxicity study in rats. This is considered a potential data gap for the assessment of hazard to infants and children, for which a 3-fold uncertainty factor was recommended.

Acute Dietary Exposure (one day):

Critical Study: Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

Executive Summary: See Section II-A, above.

Endpoint and Dose Level Selected for Use in Risk Assessment: NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

Uncertainty Factor (UF): Same as Section II-A, above.

Comments and Rationale: Although the chronic toxicity study in rats is a long-term study, it was considered appropriate to use for the acute exposure risk assessment since the endpoint selected (cholinesterase inhibition) occurs as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies.

Supportive Data: The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study. In this two-generation reproductive toxicity study, Sprague-Dawley (Crl:CD SD BR) rats, 25 per sex were treated with 0 (control), 20, 80 or 300 ppm (0, 1.5, 6.1 or 23.4 mg/kg/day) of phosmet (95.%, Lot #EHC-0866-14; WRC-4921-42- 8) in the diet continuously. Parental toxicity consisted of RBC ChE inhibition at 20 ppm (6-16%), 80 ppm (>37%), and 300 ppm

(>74%). Serum ChE was inhibited at 80 ppm (34%) and 300 ppm (65%). There were clinical signs (tremors) noted at 300 ppm). The parental LOEL is less than 20 ppm. The parental **NOEL is equal to or less than 20 ppm.** Reproductive toxicity consisted of decreased fertility, number of live pups/litter, pup weights, lactation index and fertility index (e.g., 88% versus 48%, control and high dose). **The reproductive LOEL is 80 ppm. The reproductive NOEL is 20 ppm based on decreased fertility.**

NON-DIETARY EXPOSURE:

Short-Term Occupational or Residential Exposure (1-7 days):

Critical Study: Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

Executive Summary: See Section II-A, above.

Endpoint and Dose Level Selected for Use in Risk Assessment: NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

Uncertainty Factor (UF): Same as Section II-A, above.

Comments and Rationale: Although the chronic toxicity study in rats is a long-term study, it was considered appropriate to use for the short-term exposure risk assessment since the endpoint selected (cholinesterase inhibition) occurs as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies.

Supportive Data: The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study (see executive summary under Section II-B, above).

Intermediate Term Occupational or Residential Exposure (one week to several months):

Critical Study: Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

Executive Summary: See Section II-A, above.

Endpoint and Dose Level Selected for Use in Risk Assessment: NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.
Uncertainty Factor (UF): Same as Section II-A, above.

Comments and Rationale: Although the chronic toxicity study in rats is a long-term study, it was considered appropriate to use for the shorter duration exposure risk assessment since the endpoint selected (cholinesterase inhibition) occurs as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies.

Supportive Data: The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study (see executive summary under Section II-B, above).

Inhalation Exposure (variable duration):

Critical Study: None identified.

Executive Summary: None.

Endpoint and Dose Level selected for use in risk assessment: None.

Comments: Since there are no studies available for inhalation exposure, it is appropriate to assume 100% absorption of the inhalation exposure estimates via the lungs.

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